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Citation for final published version:

Allen, Christopher M., Feng, Jenny J., Willis, Mark D. ORCID: <https://orcid.org/0000-0003-3024-6063>, McGinley, Marisa, Ontaneda, Daniel, Tallantyre, Emma C. ORCID: <https://orcid.org/0000-0002-3760-6634> and Evangelou, Nikos 2020. Clinical observation during alemtuzumab administration. Multiple Sclerosis and Related Disorders 37 , 101412. 10.1016/j.msard.2019.101412 file

Publishers page: <http://dx.doi.org/10.1016/j.msard.2019.101412>
<<http://dx.doi.org/10.1016/j.msard.2019.101412>>

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Title: Clinical observation during alemtuzumab administration

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Article type: Commentary

Word count: 601

Keywords:

20 : Therapeutics

23 : ALEMTUZUMAB (CAMPATH-1H)

Highlights:

- Alemtuzumab has been associated with stroke and cervicocephalic dissections
- Monitoring blood pressure is currently recommended by the EMA
- Monitoring blood pressure is not useful in predicting these rare side effects

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There is growing evidence regarding the risk of cervical arterial dissection and intracerebral haemorrhage immediately following alemtuzumab infusion, for relapsing remitting multiple sclerosis (MS). Durand-Dubief et al. reported a case of multiple cervical arterial dissections days after treatment with alemtuzumab.¹ Five cases of intracerebral haemorrhage were recently reported by Azevedo et al.² In November 2018, this concern prompted the United States Food and Drug Administration (FDA) to add the risk of stroke within three days of administration to the boxed warning on the drug's label.³ The FDA commented on the possible causative role of cytokine release syndrome, but decided there was insufficient evidence. The European Medicines Agency (EMA) have recently launched a safety review, placed interim restrictions on the prescription of alemtuzumab, and focussed on blood pressure, advising: "For patients being treated with Lemtrada®, vital signs should be monitored before and during the intravenous infusion."⁴ Azevedo et al. suggested that hypertension, or acute fluctuations in blood pressure, may be responsible for acute haemorrhagic strokes and proposed four criteria that should prompt admission for inpatient observation with strict blood pressure control. Either a 20% or 20mmHg increase in the mean daily systolic blood pressure (SBP), or a one-off value that exceeds the patients' baseline SBP by the same extent. Chinea et al. subsequently reported their prospective observational safety study of alemtuzumab administration and found that 39% of their cohort had a SBP \geq 160 mmHg at least once during treatment, and only half of this group had a pre-existing diagnosis of hypertension.⁵

We audited 83 consecutive patients receiving their first course of alemtuzumab therapy for MS from our three MS centres. Blood pressure was recorded prior to infusion and at 30-minute intervals for up to four hours post infusion. The cohort was 73% female; had a mean age of 36; a median EDSS of 3.0, and 27% received alemtuzumab as first line therapy. Five patients had a pre-existing diagnosis of hypertension, two were obese, two were current smokers, one was an ex-smoker and one had type two diabetes mellitus. Pre-medication given prior to each infusion consisted of methylprednisolone 500-1000mg, acetaminophen 1000mg, and diphenhydramine 50mg or cetirizine 10mg.

While there was no significant change in mean or peak SBP or diastolic blood pressure over the five infusion days (\leq 3mmHg), Azevedo's proposed criteria were met by 59% of the cohort at least once across all five days of treatment (table 1). There was no routine monitoring for evidence of cytokine release syndrome. In our cohort, there was one case of carotid artery dissection, occurring after the third day of alemtuzumab infusion in a female patient aged 25 years old. Just as with Durand-Dubief's case, she had no history of a connective tissue disorder, trauma, or a recent infection. This patient met only one of Azevedo's proposed criteria; on the day the dissection occurred the patient's SBP had a one-off value in excess of 20mmHg of that day's baseline.

Based on this data, we believe that the clinical observations suggested by Azevedo et al. and the EMA lack clinical utility in identifying people at risk of cervicocephalic arterial dissection or cerebrovascular events during treatment with alemtuzumab. The proposed criteria lack specificity due to the variability of routine clinical SBP recordings and the rarity of adverse events. We believe further safety studies are needed to help mitigate the risks of therapy, exploring the value of additional monitoring for evidence of cytokine release syndrome, not just blood pressure monitoring. Monitoring for cytokine release syndrome might include a combination of clinical observation and blood testing for markers of cytokine release such as D-dimers, prothrombin time, TNF- α , IFN- γ and IL-6.

Table 1

Proposed Criteria	Patients meeting criteria (%)
Mean daily SBP >20% pre-treatment baseline	11 (13)
Mean daily SBP >20mmHg pre-treatment baseline	13 (16)
Daily peak SBP >20% daily baseline	33 (40)
Daily peak SBP >20mmHg daily baseline	45 (54)
Meeting any of the criteria during treatment	49 (59)

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Acknowledgements

We thank the patient for consenting to have details of her case published in this commentary.

Author's Contributions

The article was conceived by NE, ECT and DO. Data collection was performed by CMA, JJF, MDW and MM. Data analysis was performed by CMA who also drafted the manuscript. All authors reviewed the manuscript for intellectual content and approved the final version.